CARDIAC INVOLVEMENT IN HEMOCHROMATOSIS

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Hemochromatosis, although a rare disease, has become well known since Trousseau originally described it.[1] Clinicians generally are aware of its clinical features, but its infrequent occurrence and varied manifestations often result in its recognition for the first time at the autopsy table. The condition has been reported with greater frequency in recent years, due, no doubt, to better clinical perception and improved methods of study.

It is not the purpose of this paper to indulge in a description of the disorder itself, since there are many excellent publications wherein it is adequately described. Rather, this discussion will deal with the cardiac changes in this disease, which have, until recently, been given scant attention. As an example, Sheldon[2] in his classic description of the condition, makes little reference to involvement of the heart, beyond pointing out that it frequently contains huge amounts of iron and that some of the reported cases died of heart failure. Blumer and Nesbit[3] point out that for some time the French have described what they believed to be an endocrinohepatocardiac syndrome in hemochromatosis that resulted in cardiac failure. However, they did not assume the failure was secondary to primary involvement of the myocardium but believed that endocrine disturbances secondary to hemochromatosis were responsible. Their patients exhibited cardiac failure at an earlier age than hemochromatosis is usually found (fourth and fifth decades); atrophy of the testes and infantilism were present; and death occurred from cardiac failure. Little support for this hypothesis has developed elsewhere and it seems unlikely

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that this syndrome represents true cardiac failure from hemosiderosis of the heart.

The name "bronze diabetes" was given to hemochromatosis by Hartman and Chausser in 1882 because of the association of a bronzed-appearing skin pigmentation with diabetes. This term has seemed to cling to this disease since as its "nom de plume." Such a characterization has tended to obscure the frequency with which the disorder does occur without pigmentation or without diabetes or both, and sometimes with overt evidences of primary cardiac disease which, in the absence of diabetes and pigmentation, can become a diagnostic problem, indeed. The first of the two cases reported herein well illustrates this point.

Althausen and Kerr[4] in 1933 suggested that, while up to that time cardiac failure had not been considered an important cause of death in hemochromatosis, the better control of diabetes would make it possible for many of these patients to live long enough to succumb from other complications of their disease. For that reason, in the future cardiac failure might be expected to assume more importance as a cause of their death. Their thoughts seem to be borne out by the increasing frequency with which myocardial involvement and failure from hemochromatosis is being reported. It seems evident now that death from myocardial failure constitutes a considerable threat to patients who have this condition.

Excess iron storage, with the resultant picture of hemochromatosis, seems to come about by three separate mechanisms:

Endogenous, increased absorption of iron. Hitherto it has been assumed that this was the only important mechanism by which hemochromatosis was produced. A poorly understood control seems to exist in the form of an intestinal mucosal block to the absorption of much more than 1 mg. of elemental iron per day. Since, in the absence of blood loss, about .5 mg. of iron is lost per day, this mechanism effectively protects the normal individual from iron excess. However, severely anemic patients can

absorb 5 mg. or perhaps more iron per day, and dietary and nutritional changes may also cause a significant increase in iron uptake.[5, 9] The exact mechanism of operation of the mucosal block still remains speculative and unknown. Granick[6] suggests that the concentration of ferritin in the mucosal cells might be important, but it is interesting that no evidence of a defect in ferritin formation has been demonstrated in hemochromatosis. It has been suggested that an inborn metabolic error may exist in hemochromatosis wherein there is a greater than normal tendency for intestinal mucosal cells to reduce iron so that it can be more easily and rapidly passed on to the circulation. An inborn metabolic defect is implied by the known occurrence of familial hemochromatosis, reported by Rogers[7] and others.

Exogenous iron, usually given by way of multiple transfusions, can be an important cause of hemochromatosis. Since each 500 cc. of normal blood contains roughly 250 mg. of elemental iron, it is easy to see how the receipt of many transfusions by patients who do not have blood loss, can result in enormous increases in storage iron. Excess iron acquired this way first seems to find its way to the reticulo-endothelial cells. Eventually, however, it is slowly redistributed in the same way as absorbed iron, thereby producing a state of hemosiderosis indistinguishable from hemochromatosis.[5, 10] It has been pointed out by Schwartz and Blumenthal[8] that not all cases of hemochromatosis following multiple transfusions have received a large amount of blood. They cite instances in which only twelve transfusions had been given over a period of nine months. It would seem that other unknown factors, such as oral iron administration, increased iron absorption in the anemic state, or nutritional factors which might alter iron absorption, must be operating as well. Cardiac failure is rarely mentioned as a complication of exogenous iron excess. Case 2 seems to represent cardiac failure secondary, at least in part, to exogenous hemochromatosis.

Nutritional, dietary, or even pancreatic disorders have been suggested as causes for increased iron accumulation by Gillman

and Gillman[9] in their detailed study of malnutrition in African natives. They demonstrated marked accumulation of iron in the liver and other tissues of African pellagrins and in natives apparently well who had subsisted on a marginal diet. They pointed out that most of the pellagrins lived on a diet consisting largely of maize. In their studies, they demonstrated that such a diet was high in iron, and when fed in the presence of a low phosphorous intake, caused abnormal absorption of iron in experimental animals. It was also found that when the pancreatic duct of cats was ligated a great increase in iron absorption took place, which indicated that in animals, at least, a deficiency of pancreatic secretion influenced the speed of iron absorption. Althausen et al[21] believe that the changes observed by Gillman and Gillman are due to a disturbance in the dietary iron-phosphorus ratio and to gross deficiency of protein, minerals and vitamins. What implication these observations may have in humans is not known. Their studies suggest the possible importance of overt or sub-clinical states of malnutrition in iron storage disease.

The following two case reports are illustrative of myocardial failure encountered as a primary cause of death in hemochromatosis. They illustrate the disease acquired in two different ways and will serve as a basis for further discussion of the problem.

Case No. 1

A 27-year old male entered the United States Veterans Hospital in Portland, Oregon for the first time October 8, 1946. He had been in excellent health until March 1944 when he first experienced easy fatigability and shortness of breath with more than usual exertion. He was in the Military Service at that time. By March 1945 he had dyspnea on ordinary exertion. When hospitalized in 1945 he was found to have auricular fibrillation and cardiac failure. He was digitalized and improved moderately. He continued this medication until his discharge in March 1946 after which he voluntarily discontinued it. At the time of his discharge from the Service such acts as climbing stairs or walking up a moderate incline would provoke shortness of breath.

In August 1946 swelling of his ankles and enlargement of his abdomen appeared and in the course of five days this swelling became very marked.

He had noticed cyanosis for at least two months and had had cough during the same time, which was not productive. An episode of hematuria and dysuria occurred at the onset of the edema and lasted three days.

His father, mother, 3 brothers and 1 sister were living and well. There was no history of familial or chronic disease in the family.

He had had the usual childhood diseases, with no sequelae, and a tonsillectomy in June 1942. He did not use drugs or alcohol and smoked moderately. Otherwise his past history was not significant.

Physical Examination: The patient was well nourished and developed, markedly dyspneic and quite cyanotic about the head, neck, chest and back. BP 120/80; P 120, with irregular irregularity. Temperature normal. His skin was normal, and outside of cyanosis, showed no pigmentation or other changes. Complete examination of the head and neck was normal except for mild swelling of both eyelids, more on the right.

Examination of the chest showed evidence of fluid in the lower half of the right thorax. The cardiac impulse could not be felt but the heart seemed enlarged. Its sounds were normal. No murmurs were detected. Auricular fibrillation was present. Quite marked distention of the peripheral neck veins without significant pulsations was evident.

His abdomen was markedly distended and there was extensive edema of the skin over it. The liver could be felt four fingerbreadths below the costal margin in the midclavicular line. No other organs were palpable. The penis and scrotum were markedly swollen and there was heavy, generalized edema of the lower extremities.

Laboratory Examination: RBC 4,760,000; Hg. 94%; WBC 7,200; PMN 93%; S.L. 7%. Urinalysis showed a trace of albumin, occasional hyaline casts, and an occasional white blood cell. No sugar was found. Pleural fluid from the right chest proved to be a transudate.

Digitalis was immediately administered and the following day his rhythm returned to normal. Electrocardiographic findings showed very low voltage in all complexes and mild changes not inconsistent with pericarditis.

X-rays of the chest (Fig. 1) showed diffuse enlargement of the heart, particularly to the left, and a right pleural effusion. The mediastinum did not seem to be displaced. Fluoroscopic examination confirmed the fact that the heart was considerably dilated in all chambers and poor movement was seen along the whole of the left border. Only moderate pulmonary congestion could be made out by x-ray.

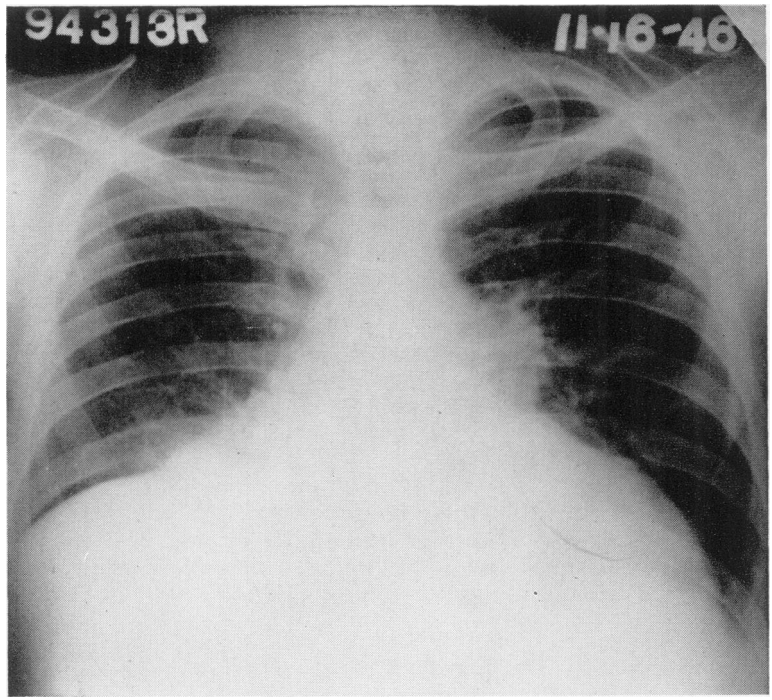

FIGURE 1 Case 1. X-ray of chest taken about one month after original hospital admission. The right pleural effusion has nearly disappeared. Gross increase in the cardiac size is obvious, as are the evidences of pulmonary congestion.

The venous pressure was recorded 170 and 188 mm. of water. Ether circulation time was 23 seconds, the Decholin circulation time 30 seconds.

Additional laboratory studies showed the blood urea to be 16.8 mg.%. The total plasma proteins were 7.5 gms.%, albumin 4.2 gms.%, globulin 3.3 gms.%. Subsequent urinalyses failed to reveal any abnormalities. Repeated electrocardiograms continued to show very low voltage of the QRST complexes, a slightly prolonged PR interval and a regular sinus rhythm.

Mercurial diuretics were added to his regime. His edema disappeared and he improved greatly. His cyanosis left and the venous distention was greatly reduced but not completely. For a time serious consideration was given to the possibility of constrictive pericarditis or pericardial effusion,

but observation failed to confirm these opinions. He was discharged November 23, 1946, considerably improved but still with a markedly enlarged heart and enlargement of the liver.

He remained at home for a month on very limited activity and sat up for only four or five hours daily. Digitalis, ammonium chloride and mercurial diuretics were continued. About two weeks after his return to his home, his dyspnea began to increase and the ankle edema returned, forcing him to be re-admitted on December 19, 1946. At this time examination again showed marked evidence of venous distention, fluid occupying the lower 2/3 of the right chest, marked cardiac enlargement with auricular fibrillation, marked hepatomegaly, moderate peripheral edema and cyanosis.

The medication previously given was continued and chest aspiration was performed. Electrocardiograms at this time showed the same low voltage. Auricular fibrillation was present. Further studies showed a cephalin cholesterol flocculation test of 3+, Takata-Ara test of 4+, and an icterus index of 7. Plasma proteins were still within normal limits. The venous pressure during this hospitalization rose as high as 192. The ether circulation time was 29 seconds, the Decholin time 32 seconds.

He improved steadily and was again discharged on February 11, 1947 with no evidence of fluid in his chest and no peripheral edema.

He was admitted to the hospital for the last time on October 16, 1947. The prescribed therapy had been followed but he had continued to be short of breath and had frequent coughing spells when he would lie down or would change position. Excessive pounding and irregularity of his heart disturbed him. He often suffered from anterior chest pain of a diffuse type and would have right upper quadrant pain when he would lie down. Paroxysmal nocturnal dyspnea had distressed him from time to time. On this admission he appeared slightly icteric.

Considerable fluid was again present in the right hemithorax. The heart was quite markedly enlarged; no murmurs were heard; the apex rate was 130; the radial rate 80—90; auricular fibrillation was present; BP 90/50. The abdomen contained a moderate amount of fluid and the liver was enlarged as before. There was considerable edema about the feet, ankles and lower legs.

Laboratory Examination: RBC 4,760,000; Hg. 94%; WBC 7,200; PMN 85%; S.L. 15%. Sedimentation rate 34 mm. (Wintrobe). Urinalysis showed a trace of albumin, an occasional hyaline cast and WBC. No sugar was found.

X-ray of the chest demonstrated a massive pleural effusion on the right with a shift of the mediastinum to the left. The heart still remained markedly enlarged.

Shortly after admission he complained of severe abdominal pain and became orthopenic and cyanotic. His temperature rose to 104.4° rectally. Subsequent to this episode, empyema appeared on the right side and a gram negative, non-motile, mutable colon organism was recovered from the blood. His white count rose to 13,000, his BUN was 20. He was treated with streptomycin and penicillin. During the next two weeks his temperature fell to normal and his white count to 5,200. A drainage tube was placed in the right pleural space from which foul, purulent material was drained.

Further laboratory studies showed total plasma proteins 6.3 gms.%; albumin 3.6 gms.%; globulin 2.7 gms.%; icterus index 6; prothrombin time varying between 37 and 87%. Repeated urinalyses remained normal. His last blood count made shortly before his death, showed RBC 4,270,000; Hg. 84%; WBC 4,500; PMN 73%; S.L. 27%; sedimentation rate 15 mm. (Wintrobe).

With anti-microbial therapy continued for six weeks, he improved. However, his electrocardiograms during this time had shown intraventricular block, periods of auricular flutter, and at other times, frequent ventricular premature beats. His treatment consisted of digitalis, a liberal supply of all vitamins and mercurial diuretics.

After this period of improvement, he began to retrogress and three weeks before his death, ankle edema, which rapidly progressed upward to involve both lower extremities, his abdomen and face, appeared. On December 27, 1947 he became extremely dyspneic, developed tachycardia of 160, a markedly diminished peripheral pulse, distended neck veins, and died the following day.

Postmortem examination was performed. Dr. Ernest J. Losli, Chief of the Laboratory Service, kindly furnished the details of this examination and a full interpretation of his findings.

At the time of postmortem no pigmentation of his skin was apparent. The liver was found 5 cm. below the costal margin in the right midclavicular line, 12 cm. below the costal border in the midsternal line and 12 cm. below the left costal border in the midclavicular line. The spleen was enlarged and extended below the costal border.

Complete atelectasis of the right lung was present, as well as a well-drained, chronic empyema cavity on that side. Outside of some congestion of the left lower lobe, the left lung was normal.

The heart was diffusely enlarged and weighed 508 grams. All the heart muscle had a somewhat brownish tinge. The mitral valve admitted 3 fingers and appeared incompetent. Left ventricle was markedly trabeculated and gave the appearance of mild hypertrophy associated with marked

dilatation. In the apical region of the right ventricle, there was a recent appearing mural thrombus and in the same area of the left ventricle a mural thrombus was present which seemed somewhat organized. Cut section of the muscle in the apical region of the left ventricle showed a hyalinized appearance. The coronary ostia were patent. The coronary vessels were traced throughout their course and were noted to be patent. No infarcted areas were seen. The foramen ovale was closed. The aorta and great vessels showed no significant changes except for a very mild amount of atherosclerosis.

The spleen was approximately 2½ times the normal size, and two areas of wedge-shaped infarcts were found in it. It was dark red in appearance when cut.

The liver weighed approximately 2,200 grams. The capsule was smooth and glistening. On cut section, it had a nutmeg appearance. The biliary tract was normal.

The pancreas was larger and heavier than normal and cut section showed a dark red color to the organ.

The left adrenal was somewhat enlarged. Cut sections of both showed a homogeneous, dark red appearance on the left, but a normal appearance on the right.

The gastro-intestinal tract, from the esophagus to the rectum, showed no significant pathological alterations.

Genito-urinary system: The kidneys were essentially normal and no obstruction or disease was found in the ureters or bladder.

Both testes were of normal size and consistency and were normal on cut section.

The thyroid was of average size and weight and showed no changes.

Microscopic examination: Heart: Multiple sections examined revealed a large quantity of coarse pigment, both within and without the myocardial fibers (Fig. 2). This pigment, with the hematoxylin and eosin stain, was yellowish, pale green, and relatively coarse. It was not limited to the paranuclear area but was found elsewhere throughout the myocardial fibers. In numerous areas the myocardial fibers had undergone complete degeneration and here the sarcolemma sheaths were present and there appeared to be pigment within them. Pigment was found in small macrophages in the interstitial tissue. Myocardial fibers showed degenerative changes in general. The nuclei of the myofibrils were enlarged and very pleomorphic. Some of them were even staghorn in shape. The pigment was not limited to the myocardium but was also found in other areas.

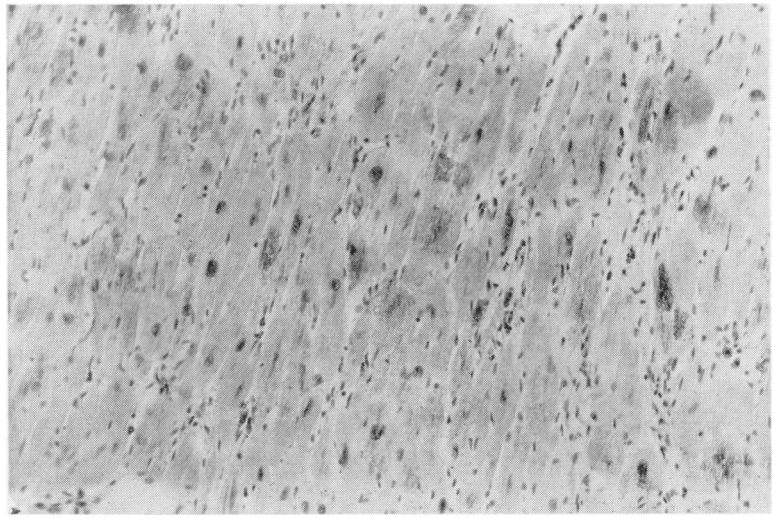

FIGURE 2 Case 1. Heart. Hematoxylin and Eosin stain. Hemosiderin deposits are extensive. Other areas showed even greater amounts than are illustrated here. Note absence of fibrosis. 175 x.

The liver (Fig. 3) showed extensive hemosiderin deposits within the hepatic cells and there was marked cirrhosis. The pigment was also present within the cells of the biliary ducts and in the connective tissue stroma. The pancreas exhibited a marked amount of fibrosis, with pigment deposits in large quantities within the pancreatic cells. Pigment was also found within the Islands of Langerhans and in the epithelial cells of the ducts. Special stains revealed extensive iron deposits in the heart, pancreas and liver.

The parenchymal cells and zona glomerulosa of the adrenals were heavily laden with the same kind of iron pigment.

Only a small amount of pigment was found in the kidney but a large amount was present in the spleen except in the area of infarction.

This case seems to fairly represent myocardial failure due to hemochromatosis. No other cause for the cardiac failure could be found. His youthful age is of great interest.

CASE NO. 2

An 11-year old, white female was admitted to the Doernbecher Children's Hospital for the last time on November 17, 1952.

She was noted to be pale at the time of birth, and at 3½ months of age, because of a rapid decline in her condition, she was brought to a physician and was found to have a hemoglobin of 10%. She was given a transfusion of blood. From this time on the child continued to have a chronic anemia which subsequent bone marrow studies indicated was due to congenital erythrocytic hypoplasia. At no time in the course of her illness was there evidence of any deficiency of the granulocyte series. She was maintained through the years with transfusions and always demonstrated anemia which was repeatedly corrected by transfusions.

The child had been normal at birth and weighed six pounds, twelve ounces. She was able to sit up at the age of six months. Nutrition was somewhat of a problem in her case; however, she continued to develop fairly normally but was smaller than normal for her age.

Outside of the anemia, she had had no other important illnesses. At age 5 she had chicken pox and her liver was palpable for a time following this, but the enlargement subsided. In January 1952 she had an illness in which her liver became enlarged briefly but receded in size.

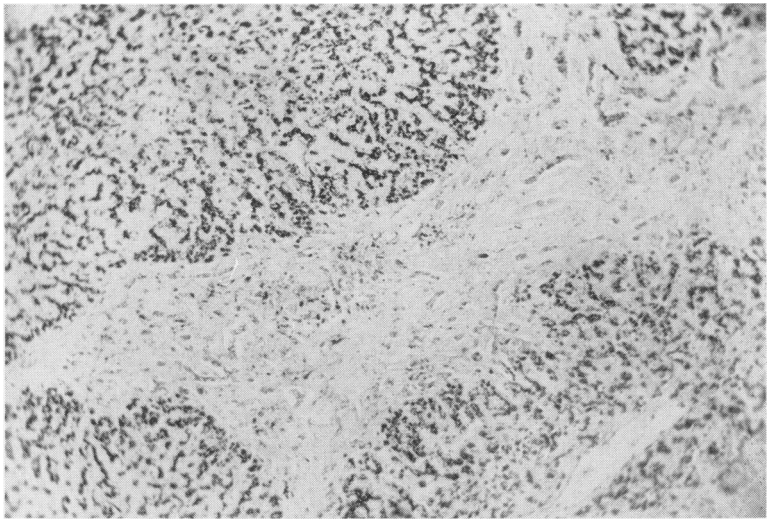

FIGURE 3. Case 1. Liver. Iron Stain. Extensive cirrhosis with heavy iron pigment concentration in the parenchymal cells. Little iron is evident in the scarred areas. Sections of the pancreas showed similar changes in the whole organ. 100 x.

Up to the time of her death she had received 69,570 cc. of blood by transfusion. No serious reactions had occurred with the transfusions, although brief febrile episodes were not rare following many of them.

All manner of therapy was tried, including iron, Cortisone and cobalt, but none were successful. Cortisone was last discontinued in December 1951.

About two years before her death her skin began to appear somewhat slate-colored and this pigmentation slowly increased.

Numerous urinalyses had been made and at no time had any abnormalities been found.

In July 1952 her liver began to be painful and was found to be quite enlarged. In September swelling of the hands and ankles was noticed. In October tachycardia was apparent and, because heart failure was felt to be present, she was treated with mercuhydrin and digitalis. However, her liver continued to remain large and painful and dyspnea, as well as edema, appeared and grew worse.

Physical Examination: Blood pressure 95/70; Pulse 120, regular; temperature normal. The patient had a dusky-gray appearance to her skin and was listless. The head and neck showed no significant abnormalities. The lungs were normal. The heart was enlarged to the left and there was a systolic murmur 2 cm. to the left of the sternum in the fifth intercostal space. The liver was enlarged to the level of the umbilicus, was quite tender but seemed smooth. The spleen could not be felt. There was marked pitting edema of both lower extremities and pitting edema in the lower back area.

Laboratory Examination: RBC 1,690,000; Hg. 5.3 grams; WBC 4,500; PMN 77%; S. L. 14%; Mono. 9%; sed. rate 40 mm. in 45 min. (Westergren); color index 1.12; volume index 1.06; saturation index 1.07; serum bilirubin 2.7 mg.%; prompt direct 1.8 mg.%. Total plasma proteins 7.2 gms.%; albumin 5.2 gms.%; globulin 2.0 gms.%.

Shortly after admission she began to have severe abdominal pain without nausea or vomiting. Her pulse rate was 136 and her blood pressure became unobtainable.

A transfusion of 200 cc. of blood was given with great difficulty in the external jugular vein. Her blood pressure had risen to 80/60 by the following morning. On November 20, 1952 her blood pressure was 70 mm/?; her pulse rate 120. X-ray of the chest showed marked general cardiomegaly, associated with exaggeration of the hilar and bronchovascular

shadows, consistent with the appearance of cardiac decompensation and acute passive pulmonary congestion (Fig. 4). An electrocardiogram showed runs of ventricular tachycardia interposed between brief periods of sinus rhythm. QRST complexes during the periods of sinus rhythm were somewhat widened and of very low amplitude.

She was continued on digitalis but during the day her liver became more tender and the edema seemed to increase. Shortly thereafter she began to expectorate foamy sputum and suddenly expired.

At autopsy examination there was extensive hemosiderosis of the liver, spleen, lymph nodes, skin, pancreas, adrenals and heart. The heart was

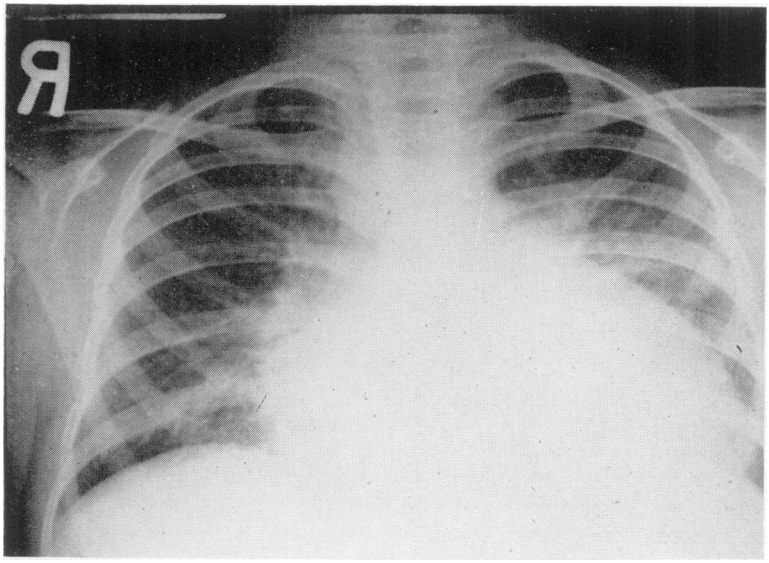

FIGURE 4 Case 2. X-ray of the chest taken shortly before death. Marked cardiac enlargement and pulmonary congestion. Some of the increase in the size of the cardiac silhouette may have been due to pericardial fluid.

dilated, exhibited moderate hypertrophy and weighed 240 grams. There was general anasarca with massive ascites. A moderate pericardial effusion, pleural effusions and pulmonary edema were present. Both adrenal cortices showed diffuse atrophy thought to be the result of prior Cortisone therapy.

Microscopic examination was made by Dr. Terence Cochran of the Department of Pathology. Heart: (Fig. 5) Numerous sections of the heart, both from the right and left ventricles, and atria, showed considerable brown pigment, which gave a positive Prussian blue reaction, indicating it to be hemosiderin. Most of this pigment was seen within the cytoplasm of the muscle cells. The other appreciable changes consisted of considerable variation in cell size, particularly apparent in cross-sections, with bizarre and variably sized cell nuclei. Striations were still evident. Although there were some fine vacuolations within the sarcoplasm of the cells, these were negative for netural fat and might have been simply artefacts. Occasional cells showed very large square nuclei, indicating hypertrophy and the

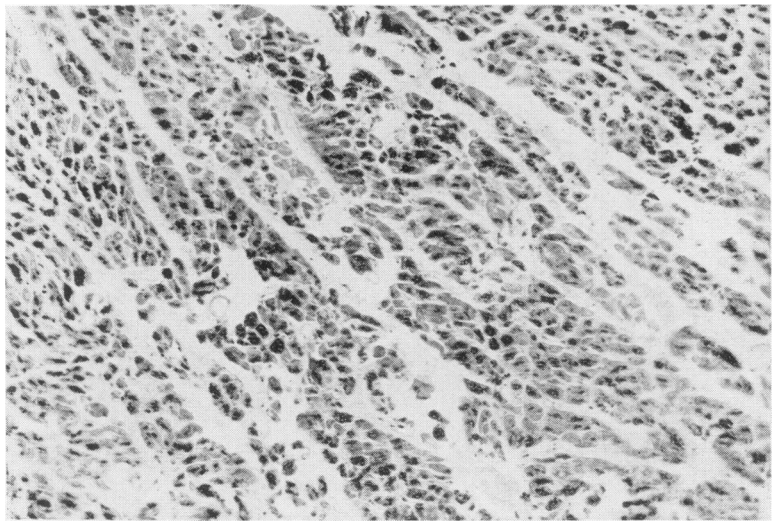

FIGURE 5 Case 2. Heart. Iron stain. The heavy iron deposits visible in the muscle cells were widespread. No fibrosis was present. 175 x.

focal small cells were interpreted as being atrophied. No appreciable scarring was seen. The most striking variations in cell size were seen in the right ventricle.

Liver: (Fig. 6) The liver showed extensive nodular cirrhosis with broad interlacing bands of scar, predominantly periportal in distribution. Within this scar tissue there was a very heavy deposition of brown pigment, both intracellular and extracellular, which stained positive for hemosiderin by the Prussian blue reaction. There was also extensive bile duct proliferation and some isolated, infiltrated inflammatory cells, including granulocytes

and mononuclear cells. The intervening liver parenchymal cells showed a loss of their usual relationship to any identifiable central vein. There was very little fat apparent in these cells; the cytoplasm was basophilic with increased basophilic stippling and also showed some iron-staining pigment. It was not nearly so marked, however, in the parenchymal cells as in the intervening scars. Most of the Küpfer cells were well outlined with hemosiderin pigment, as well. At one point within the liver, there was a circumscribed, small nodule, 3 mm. in diameter, which was identified as an adenoma. The cells in this adenoma, although containing hemosiderin, showed an appreciably less amount of iron pigments as compared to the adjacent cirrhotic liver.

Pancreas: The pancreas showed considerable autolysis and widespread infiltration between the various lobules of fat. It could be appreciated, however, that there was extensive iron-stained pigment within the scar tissue, which formed a fine network throughout the lobules, as well as within the parenchymal cells and the cells of the islets.

Kidney: The kidney showed no appreciable change, except for extensive iron-staining pigment within the tubular epithelium, particularly of the

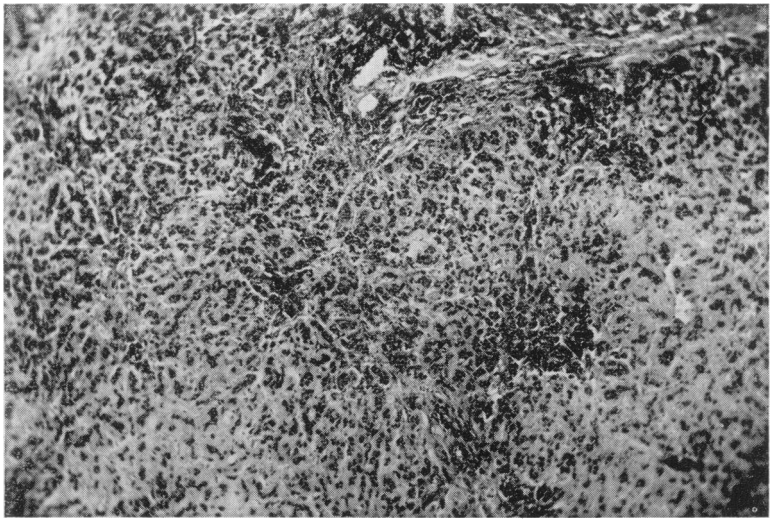

FIGURE 6 Case 2. Liver. Iron stain. The relatively greater concentration of iron pigment in the Kupfer cells and regions of fibrosis, often the case in exogenous hemochromatosis, is clearly shown. The cellular content of iron was, however, high. The pancreas showed similar changes throughout all parts of the organ. 100 x.

distal convoluted tubules, the loops of Henle, and probably the first portion of the collecting tubules.

Bone Marrow: Numerous sections of the bone marrow showed normal cellularity with normally appearing and occurring megakaryocytes, as well as adequate granulopoiesis. Areas of erythropoiesis, however, were difficult to find and undoubtedly were decreased. Occasionally there were aggregations of lymphoid cells as well. Iron stains revealed a moderate amount of Prussian blue positive pigment within the bone marrow. It certainly was not as marked there, however, as in the other organs. Sections of the other tissues, including small and large intestine, adrenals, lymph nodes, thyroid and hypophysis all showed abundant iron-staining pigment.

This case strikingly demonstrates hemosiderosis from exogenous sources, probably exaggerated some by the effects of anemia. It could be fairly argued that her terminal cardiac failure might be the result of chronic anemia and high cardiac output consequent upon it. However, she was not severely anemic all the time, she had no other complicating heart disease, and cardiac failure appeared suddenly after many years of management. The failure, once started, was rapidly progressive. These observations together with the histological studies would seem to make tenable the assumption this child died, for the most part, of hemosiderosis of the heart. The ventricular tachycardia was not thought to be due to digitalis intoxication.

The evidences of cardiac change in hemochromatosis are usually those of diffuse cardiac enlargement eventually followed by a rapidly progressive myocardial failure. A few patients have complained of exertional precordial and substernal pain. No coronary sclerosis adequate to explain this was subsequently found.[3, 17] Once myocardial failure has made its appearance, few cases live beyond 9-12 months, although instances have been recorded of longer life, as in case 1 reported here.

When myocardial failure appears it seems to be whole-heart failure, in that both sides are simultaneously involved. Rightsided failure tends to predominate. As a result edema is a prominent finding and is often marked. The heart is found on examination to be moderately or even greatly diffusely enlarged. Murmurs are

usually absent. No significant changes in blood pressure are noted except for a general tendency toward normal or hypotensive levels.

Of considerable interest is the high incidence of arrhythmias and blocks in the reported cases. These findings appear to be present in a much higher ratio than is ordinarily seen in myocardial failure due to other causes, with the possible exception of coronary arteriosclerosis. Paroxysmal auricular tachycardia, auricular flutter, and auricular fibrillation include the tachycardias reported. Ventricular tachycardia seems to be exceedingly rare.[4, 13, 14, 15] It was found in our second case as a terminal manifestation. Conduction disturbances include partial auriculo-ventricular block and complete auriculo-ventricular block with dissociation.[4, 12, 17]

Electrocardiographic changes, outside of those produced by the arrhythmias and blocks, are not striking in degree but have been numerous. These have consisted, for the most part, of a tendency for low voltage of the QRS complex and the frequent occurrence of flattened or diphasic T waves in leads other than standard Lead III. No significant T wave inversions and no striking deviations of the ST segment have been encountered, as far as can be determined.[4, 14, 16] Sino-auricular block was reported once. Premature beats of ventricular and auricular origin have been common.

The clinical diagnosis of myocardial failure due to this cause, is not difficult if it occurs in association with the other classical evidences of hemochromatosis, such as cirrhosis of the liver, pigmentation of the skin, and diabetes. A steady, inexorable progress of the cardiac failure accentuates this diagnosis even more. In instances, such as our case 1, where the cardinal corollary signs and symptoms are missing or poorly developed, the diagnosis of hemochromatosis heart disease may become extremely difficult. While this type of heart disease, without the usual findings of hemochromatosis, must be considered exceedingly uncommon,

nevertheless it is worthwhile to consider it in any individual who presents progressive whole-cardiac failure that does not respond well to treatment and when a cause cannot be with certainty determined. In these circumstances an accessory aid, such as examination of the bone marrow for the presence of hemosiderin clumps, is of real value.[5] Determination of the serum iron and estimation of the degree of saturation of the iron carrying protein, siderophylin, is also helpful. In hemochromatosis the serum and siderophylin almost invariably will be found saturated with iron.[6] Liver biopsy demonstration is, of course, one of the strongest bits of evidence of the existence of this disease, but may be hazardous in the presence of myocardial failure with hepatic congestion.

Pathological study of the heart in hemochromatosis has failed to explain adequately the cause of myocardial failure. No coronary artery disease of note has been described. The heart muscle uniformly has a brownish color and the total heart mass is very often increased in amount, sometimes considerably. Evidences of mild hypertrophy are often seen and dilatation of all the cardiac chambers, more particularly the right, is the rule. Mural thrombi, without evidences of underlying infarction, have been reported from time to time in either or both ventricles and clots have also been described in the auricular appendages.

Histologically, a variety of changes are seen. Most outstanding are the deposits of hemosiderin pigment in the heart muscle fibers. The pigment in them is clustered most heavily about the nuclei in a polar distribution that extends from the nuclei in a linear manner toward the ends of the cell for varying distances. All phases of degenerative changes in the cells may be seen—swelling, hydropic changes, atrophy, splitting and fissuring of the muscle fibrils, loss of the muscle striations, pyknosis and karyorrhexis. Some cells show complete loss of sarcoplasm with only the sarcolemma remaining and enclosing a mass of granules of hemosiderin. This change was seen prominently in Case 1.

[3, 4, 11, 13, 15] Fatty degeneration of the muscle has been described.[17]

Fibrosis of the myocardium is by no means universal. Some cases that have had severe failure show almost no fibrosis. Others have exhibited myofibrosis, occasionally of severe degree.[3, 11, 13] Many observers have described hemosiderin granules in histiocytes, mononuclear cells, and in areas of definite fibrosis. However, usually little hemosiderin is found outside the muscle cells. No correlation can be made between the intensity of the hemosiderosis and the occurrence of fibrosis. In some of the hearts with the heaviest iron deposition, fibrosis was minimal or absent. Occasionally interstitial edema is noted.[15] Thickening of the pericardium of slight amount has been found occasionally but never to an important degree. Areas of fibrosis of a patchy type have been described. These have not been due to vascular injury, as far as could be determined. No adequate studies of the conduction bundles have been made.

Some hearts show abnormally large amounts of hemosiderin and yet have not undergone failure, in contrast to some which show lesser amounts of hemosiderin and have been in advanced failure. Such a circumstance may be, in part, the result of the factor of time since some patients with advanced hemochromatosis die of hemorrhage, liver insufficiency or other complications before they may have had time to develop the myocardial failure that would have appeared later.

It seems likely that the simple storage of iron in cardiac muscle in the form of ferritin and hemosiderin does not, in itself, cause irritation, subsequent degeneration of the fibers and replacement fibrosis.[6] In the light of the failure of anatomic changes to adequately explain the myocardial failure, some other cause, such as a derangement of cellular physiology and chemistry, due to an excess of iron, might well be at the root of the cardiac weakness.

Ferritin is a protein substance which contains within its structure clusters of micelles of polymerized masses of ferric hydroxide.

It exists in normal heart muscle in small amounts or not at all. In hemochromatosis considerable concentrations are found. Hemosiderin is made up of large clusters of iron hydroxide groups which are mixed with some type of protein. Recent evidence[22] indicates that it may be composed of sizable aggregates of ferritin which tend to accumulate when iron stores are excessive. These aggregates become large enough to be visible microscopically, can be stained for iron and may contain as much as 35% by weight of the metal.[6] Hemosiderin iron is available for use, as is ferritin iron. However, when it exists in such large amounts as to interfere with cell function its mobilization is impaired.[5, 22]

Large amounts of hemofuscin and melanin are characteristically found in hemochromatosis, but there is no evidence that either of these pigments plays any part in the disturbance of the heart or other structures.

Racker and Krimsky[18] demonstrated with brain homogenates, that exceedingly small amounts of ferrous sulfate would partially inhibit the enzyme glyceraldehyde phosphate dehydrogenase. This enzyme acts rather far down in the glycolytic cycle but its inhibition would decrease the formation of the high-energy adenosine triphosphate (ATP). ATP is necessary for the proper phosphorylation of glucose. These investigators found that some effect, presumed to be due to a decrease in ATP, reduced the formation of fructose-1-6-diphosphate. Inhibition along this earlier part of this chain of reactions would further limit the amount of ATP formed. If it can be presumed that excess iron stores in heart muscle have a similar effect upon the glycolytic cycle in its cells, a profound effect upon heart muscle metabolism would result. It seems reasonable, too, that insoluble iron phosphate compounds may be precipitated from phosphate-containing proteins in the sarcoplasm, the nucleo-proteins of the nucleus and from ATP in the presence of excess cellular iron. No proof of such changes exists at present. Certainly, the swelling, hydropic degeneration, atrophy, vacuolization, fibrillation and fatty changes in the heart muscle cells suggest some kind of biochemical disturbance.

Treatment of these cases is unsatisfactory. The usual measures applied to the treatment of congestive heart failure with edema are effective to one degree or another for a while, but eventually, as was true in both our cases, such measures eventually fail. The effects of the removal of iron stores by repeated bleeding is under study at the present time by numerous investigators.[5] Removal of large quantities of iron can be accomplished this way but it is uncertain at present as to what effect this will have on the over-all disease. Such a form of therapy, which requires a prolonged period for any definitive effect, would hardly be applicable in cases of heart failure that are of such short duration. Recognition of the possibility of heart injury before the stage of irrevocable tissue damage might make constructive results possible, but judgment of this method of therapy must await further investigation.[5, 19, 20]

Summary

The mechanism of excess iron storage in the body is reviewed.

Three reasons for such excess iron stores have been advanced: *endogenous* because of increased intestinal absorption due to unknown causes; *exogenous* by way of multiple transfusions; and *nutritional or dietary* disturbances which may enhance iron absorption.

Clinical and pathological features of the whole heart failure seen in hemochromatosis are discussed.

Simple irritative injury to cardiac muscle cells by hemosiderin deposits seems inadequate as an explanation for cardiac failure. Biochemical changes in important enzyme systems and the destruction of phosphate-containing protein substances in the sarcoplasm and nucleus by the excess iron may be a cause for the myocardial failure.

REFERENCES

1. TROUSSEAU, A.: Clinical Medicine, 1868-1872, New Sydenham Society, Vol. III, pp. 500-502.

2. SHELDON, J. H.: Haemochromatosis, London, 1935, Oxford University Press.

3. BLUMER, GEORGE, and NESBIT, ROBERT R.: A Case of Hemochromatosis with Degeneration of the Heart Muscle and Death from Congestive Heart Failure. New Eng. Jour. Med. *218:* 295-298, February 17, 1938.

4. ALTHAUSEN, T. L., and KERR, WM. J.: Hemochromatosis II. A report of Three Cases with Endocrine Disturbances and Notes on a Previously Reported Case. Discussion of Etiology. Endocrinology *17:* 621-646, Nov.-Dec. 1933.

5. FINCH, CLEMENT A., HEGSTED, MARK, KINNEY, THOMAS D., THOMAS, E. D., RATH, CHARLES E., HASKINS, DONALD, FINCH, STUART, FLUHARTY, REX G.: Iron Metabolism. Blood *5:* 983-1008, Nov. 1950.

6. GRANICK, S.: Iron Metabolism and Hemochromatosis. Bull. N. Y. Acad. Med. *25:* 403-428, July 1949.

7. ROGERS, WALTER F., JR.: Familial Hemochromatosis: With Comments on Adrenal Function in Hemochromatosis. Amer. Jour. Med. Sci. *220:* 530-537, Nov. 1950.

8. SCHWARTZ, STEVEN O., and BLUMENTHAL, LUNOLL A.: Exogenous Hemochromatosis Resulting from Blood Transfusions. Blood *3:* 617-640, June 1948.

9. GILLMAN, JOSEPH and GILLMAN, THEODORE: Perspectives in Human Malnutrition. New York, 1951. Grune and Stratton.

10. NORRIS, ROBERT P. and MCEWEN, F. J.: Exogenous Hemochromatosis Following Multiple Blood Transfusions. Jour. Am. Med. Assn. *143:* 740-741, June 24, 1950.

11. KESCHNER, HAROLD W.: The Heart in Hemochromatosis. South. Med. Jour. *44:* 927-931, October 1951.

12. TUCKER, H. ST. GEORGE, JR., MOSS, LLOYD F., WILLIAMS, J. POWELL: Hemochromatosis with Death from Heart Failure. Am. Heart Jour. *35:* 993-1000, June 1948.

13. GRIFFIN, W. R., NELSON, H. G., SEAL, J. R.: Hemochromatosis with Auricular Fibrillation. Am. Heart Jour. *39:* 904-908, June 1950.

14. BOTHWELL, T. H., VAN LINGEN, B., ALPER, T., and DU PREEZ, M. L.: The Cardiac Complications of Hemochromatosis. Am. Heart Jour. *43:* 333-340, March 1952.

15. LEVIN, EUGENE B., and GOLUM, ABRAHAM: The Heart in Hemochromatosis. Am. Heart Jour. *45:* 277-288 February 1953.

16. SWAN, W. G. A. and DEWAR, H. A.: The Heart in Hemochromatosis. British Ht. Jour. *14:* 117-124, 1952.

17. PETIT, DONALD W.: Hemochromatosis with Complete Heart Block. Am. Heart Jour. *29:* 253-260, February 1945.

18. RACKER, E. and KRIMSKY, I.: Inhibition of Coupled Phosphorylation in Brain Homogenates by Ferrous Sulfate. J. Biol. Chem. *173:* 519-533, April 1948.

19. HASKINS, DONALD, STEVENS, ALEXANDER R. JR., FINCH, STUART, FINCH, CLEMENT A.: Iron Metabolism. Iron Stores in Man as Measured by Phlebotomy. Jour. Clin. Investig. *31:* 543-547, June 1952.

20. HOUSTON, J. C.: Phlebotomy for Haemochromatosis. Lancet *264:* 766-768, April 18, 1953.

21. ALTHAUSEN, T. L., DOIG, R. K., WEIDEN, S., MOTTERAM, R., TURNER, C. N., MOORE, A.: Hemochromatosis. Arch. Int. Med. *88:* 553-570, November 1951.

22. SHODEN, ARNE, GABRIO, BEVERLY WESCOTT, FINCH, CLEMENT A.: The Relationship Between Ferritin and Hemosiderin in Rabbits and Man. Jour. Biol. Chem. *204:* 823-830, October 1953.

DISCUSSION

DR. ROBERT L. LEVY (New York): As Dr. Lewis spoke, it occurred to me that there might be an analogy between these cases and certain others showing cardiac enlargement of obscure cause. I refer to von Gierke's glycogen disease and, more particularly, to so-called idiopathic myocardial hypertrophy. In the latter condition we have been actively interested for a number of years.

In the idiopathic group, as in these cases, there is great cardiac enlargement. Other clinical features are the occurrence of arrhythmias of various sorts; the formation of intracardiac thrombi with embolization to the lungs or periphery; and the likelihood of a fatal outcome within a year after the

onset of symptoms. At autopsy, the lesions in the heart vary from simple hypertrophy of the muscle fibers to areas of focal necrosis and extensive replacement fibrosis.

I have referred to certain points of similiarity between these conditions because, although their etiology is unknown, it seems possible that there may exist some metabolic fault, probably different in each, which is responsible for the pathologic lesions and, eventually, for heart failure.

DR. HOWARD F. ROOT (Brookline, Mass.): To me, this paper is of very great interest, and perhaps to others who see many diabetic patients.

Within the last few years, in our series of patients with hemochromatosis and in our series associated with diabetes, including some forty-five or fifty patients—and I recall, while sitting here, five patients in this group (which, you see, is roughly 10 per cent) who have died characteristically with heart failure. Two were young, in their thirties.

If you will remember the history of hemochromatosis, and at least its interpretation as a chronic congenital iron-retention process going over the years, one expects its development early in life.

These two both illustrated hemochromatosis with a rather rapid development of heart failure, completely resistant to any form of treatment, so that we have, on the basis of those two cases alone, come to the feeling that, when one finds without other explanation, rapidly progressing heart failure with a large heart with failure to respond to any treatment hidden hemochromatosis is worth bearing in mind, not only for diabetics but for others.

In this group, it has been our experience that the level of serum iron has proven actually more reliable, in terms of percentage, as an indication of hidden hemochromatosis, than some other diagnostic procedures, including the skin test, urinary test, and so on.

One of these patients, however, instead of being in the thirties, was in the seventies. That is rather late for the development of hemochromatosis.

That patient was not diagnosed, except by the serum-iron level. There was a good deal of doubt in our minds what the patient really had. The patient finally died, and proved to have hemochromatosis plus a large liver tumor.

In our patients, the hearts have shown considerable change, as you have described; but fibrosis has also been a very striking feature in them.

I merely add this little personal experience to emphasize that which Dr. Lewis has already said; namely, that this problem is not quite so rare as it has been thought to be and, at least in our experience, hemochromatosis seems to be, in recent years, much more frequently associated with severe heart disease, even though it may not have been fatal, than formerly.

DR. CYRUS C. STURGIS (Ann Arbor, Michigan). Some years ago I observed a patient, a male, eighteen years of age, with idiopathic aplastic anemia who was given 138 blood transfusions in four years. Each transfusion averaged 500 c.c. of blood, and hence a total quantity of 68,500 c.c. was administered. As hemoglobin contains 0.344 per cent of iron, it would mean that 36.74 grams of iron were injected intravenously during this period. Toward the end of the four years, it was noticed that the patient's skin had a distinct grayish color, and biopsy showed a deposition of iron. At this time the patient developed a partial heart block which later proceeded to complete block with eventual chronic congestive failure and death. Necropsy showed a deposition of iron in almost all of the organs of the body including the heart. It contained iron in the myocardium and in the Bundle of His. As there is convincing evidence that in the male only traces of iron are eliminated in the urine and bile, it is possible that the iron in the injected hemoglobin accounted for the presence of the metal in the tissues. It should also be considered, however, that the deposition of iron throughout the body in patients with aplastic anemia may result from hemorrhage or hemolysis.

DR. JOHN MINOR (Washington, D. C.): I just want to make one comment about Dr. Lewis' very interesting paper, to ask a question really. He has shown us another obscure cause of myocardial failure.

Ordinarily, congestive failure is considered to be a contra-indication to needle biopsy of the liver. I wonder whether sometimes, in circumstances such as his first case, where there was no pigmentation and there was no diabetes and difficulty of diagnosis was obvious, he would consider it justifiable to subject this patient with congestive failure to a needle biopsy of the liver, and thereby obtain a diagnosis which might lead, sometimes, to effective therapy.

DR. THOMAS FITZ-HUGH, JR. (Philadelphia): Mr. President, I just want to record one presumably favorable point in the exogenous type of hemochromatosis.

I reported before this Society, about three years ago, the case of a man who had had approximately 100 transfusions in the course of a year, for intractable anemia which had apparently not been properly assessed. We undertook splenectomy for hemolytic anemia, at which time hemochro-

matosis, which was clinically obvious, was proven by liver and spleen specimens which I showed before this Society a few years ago.

The problem of his anemia was solved by splenectomy. He has since remained perfectly well, except for his diabetes, which is stationary. His cardiac status has also remained stationary. He had the flat T waves and the small RST complexes which have been described. He had some effort chest discomfort which has cleared up.

It is probable that, had this man gone on receiving blood transfusions, he would have developed the full-blown pattern of cardiac failure which has been described here; but his anemia problems having been solved by splenectomy, it looks as if he is going to remain alive and well, thus suggesting that the hemochromatosis heart damage is not necessarily progressive and fatal.

DR. FRANCIS C. WOOD (Philadelphia): It just occurred to me that, when you see an adolescent who has been chronically anemic, he almost always has considerable cardiac enlargement.

I wonder if there is a pediatrician or hematologist in the room who could tell us whether such a series of patients, at autopsy, will show that hemochromatosis is partly a cause of that cardiac enlargement.

DR. CECIL J. WATSON (Minneapolis): I have enjoyed Dr. Lewis' presentation very much. I wonder if, in his reading about hemochromatosis and the heart, he has encountered any mention of hemopericardium.

Quite a few years ago, indeed well before we had any knowledge of the relation of prothrombin to bleeding in patients with liver disease, we had a patient on our ward, who was deeply pigmented, generally bronzed, who had the picture of heart failure. He had marked edema of the legs, high venous pressure, enlarged liver, but no diabetes. On pericardial tap, almost pure blood was obtained from the pericardial cavity.

He improved markedly after this, in surprising fashion, and went home without any definite diagnosis. That was before the days of liver biopsy which, I am sure, would have established the diagnosis.

It should also be mentioned that his skin, although deeply pigmented, failed to show any evidence of iron. I would just emphasize, with respect to this point, that Lubarsch, in a large series of cases of hemochromatosis proven subsequently at autopsy, found that only about 50 per cent had demonstrable iron in the skin.

We have had the same experience on a number of occasions. There is no stainable iron, but only a brown melanin-like pigment.

This patient returned several years later in moribund diabetic coma and, at autopsy, had a widespread hemochromatosis but no further hemopericardium.

At that time, I was able to find two instances in the French literature—I am sorry I cannot remember the names of the individuals who reported the patients—in which hemopericardium had been noticed in association with hemochromatosis.

DR. THOMAS MCP. BROWN (Washington, D. C.): Several years ago, Dr. Sossman reported the unusual ability of the iron-laden, pigment-laden liver, to obstruct x-ray radiation; and, as you may remember, showed beautiful x-rays showing a double line in the right diaphragmatic area.

Dr. Lewis has indicated that it is very difficult to diagnose this condition. One wonders whether Dr. Sossman's idea might not be utilized with penetrating x-ray irradiation of the cardiac shadow, which should render a more dense shadow, even with penetrating x-ray, than normally.

DR. LEWIS (Closing): In regard to Dr. Levy's remarks, there is an interesting analogy between von Gierke's disease and idiopathic hypertrophy, which suggests that in both some fundamental biochemical and physiologic change has taken place.

I was interested in Dr. Root's young patients. The first case I reported was quite young to have had so far advanced hemochromatosis, especially because of the known time usually required for such an increase in stored iron.

I think Dr. Root made an important point, too, in the matter of the hidden hemochromatosis. In my first case, the cause of the heart disease was not recognized by anyone. As a matter of fact, for a long time serious thought was given to the possibility of pericarditis of a constrictive type.

The serum-iron values certainly are useful; and also, if one is in a position to do so, is estimation of the quantity of iron in the iron-carrying proteins.

Fibrosis of the myocardium has been mentioned by a number of people. However, I have been impressed, after review of a large number of reported cases, that fibrosis is really not an outstanding feature.

In regard to Dr. Sturgis' case, I remember this case well, having read or heard of it before.

Dr. Minor, I am not sure. Personally, I would be fearful of doing a liver biopsy in the two cases I reported, because of the congestion in the

liver which was present. Some who are highly proficient in that technique might feel differently about it.

With regard to Dr. Fitz-Hugh's remarks about blood transfusions, it is interesting that there have been a fair number of cases of hemosiderosis reported in which not too much iron had been given by transfusion. These examples occurred in people with prolonged anemia. There have been observations made by Gillman and Gillman, and other people, which suggest that in the presence of severe anemia iron absorption is increased, and that also there may be nutritional and dietary factors present, too, which contribute to abnormal absorption of iron. It is therefore possible that in a person with a chronic anemia of long standing, other factors than the simple parenteral administration of blood may be important.

We gave serious thought to the matter of whether anemia could fundamentally be behind this second case of myocardial failure. We discussed it with our hematologists, who had followed this patient. In their opinion it would be highly improbable that a high-output failure could be the cause of the myocardial failure. They had never encountered high output failure due to anemia in so young a patient.

I have never seen a case of hemopericardium in this disease; I only know the reference to it which Dr. Watson mentioned. Apparently it is an uncommon happening.

I think Dr. Watson made a significant point that the pigmentation in hemochromatosis is sometimes not due to iron, but to excess melanin which is formed in this disease.

In the matter of increased density of the heart shadow by x-ray as a diagnostic sign, I rather question whether it would ever be as useful as it sometimes is in the case of the liver. When the heart is large, I think one would have a very hard time deciding about this.